DISSERTATION ON PERIPHERAL NERVE DYSFUNCTION STUDY IN CHRONIC KIDNEY DISEASE

M.D. DEGREE EXAMINATION BRANCH – 1
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CERTIFICATE

This is to certify that this dissertation entitled "PERIPHERAL NERVE DYSFUNCTION IN CHRONIC KIDNEY DISEASE" is a bonafide record of work done by DR. M. LAKSHMI PRIYA under my guidance and supervision in Tirunelveli Medical College Hospital during the period of her post graduate study for M.D. (General Medicine) from 2004 -2007.

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AIMS OF THE STUDY

This study is aimed:

1) To evaluate the incidence of overt neuropathy and subclinical neuropathy in chronic kidney disease patients attending our hospital.

2) To evaluate the clinical manifestations of peripheral nerve dysfunction in chronic kidney disease patients attending our hospital.

3) To correlate the incidence of peripheral neuropathy with reference to the severity and duration of the chronic kidney disease.

INTRODUCTION

Peripheral nerve dysfunction is a recognised complication of chronic kidney disease Most of the time, patients who are having features of peripheral nerve dysfunction won't come out with complaints of it, unless it is specifically asked or looked for. Since the year 1962 various authors have already discussed about the prevalence, incidence, clinical features and pathology of peripheral nerve dysfunction in chronic kidney disease.

In our hospital, more than 1000 patients for 2 years fulfilling the criteria for chronic kidney disease are treated as inpatient or outpatient.

At present the medical treatment for kidney disease is improving and patient's long term survival is improving. Peritoneal dialysis, heamodialysis and transplantation have revolutioned the prognosis of chronic Kidney disease in recent periods. As patients life span is prolonged due to recent improvement in treatment of chronic kidney disease, it is essential to know about the complication that can occurr in patient surviving for long period with chronic kidney disease of which peripheral nerve dysfunction is one of the recognizable and treatable complication of chronic kidney disease. The Etiology of chronic kidney disease is varying in nature, but the clinical symptoms and signs are of same.

The study mainly focuses the incidence, clinical manifestation and severity of peripheral nerve dysfunction in patient with chronic kidney disease admitted in out hospital.

HISTORICAL REVIEW OF THE LITERATURE

A decade ago the first experimental programs in haemodialysis for chronic kidney disease were in progress. Hegstrom and coworkers (1962)[14, 15] in Seattle, noted that all their original four patients developed some signs of polyneuropathy, one to a disabling degree. There was grave concern at first that the procedure of dialysis itself might be culpable, but intensifying dialysis produced some amelioration. At about the same time, Asbury victor and dams (1962, 1963)[16, 17] described the clinical and pathologic features of polyneuropathy associated with chronic kidney disease in four patients. The important points about these cases were, first, that none of the patients had undergone haemodialysis, and second, that the basis for kidney disease was diverse, including chronic obstructive uropathy with pyelonephritis, chronic glomerulonephritis, and hereditary interstitial nephritis. Thus, it appeared that chronic kidney disease could by itself be responsible for polyneuropathy, and haemodialysis was absolved of being the primary offender.

In an earlier report, Martin and Tyler (1961) also had described severe polyneuropathy, in two young men with hereditary interstitial nephritis, although they thought the neuropathy was related to the underlying hereditary disorder rather than being due to the uremic state. Both their patients underwent dialysis, but only after the neurologic symptoms were well established.

More recently, in a prospective study of patients with relatively mild renal insufficiency who were treated conservatively without dialysis, Hebsen, takeoff, and Honet (1967)[18] showed that rising serum creatinine levels correlated with decreasing motor nerve conduction velocity. Clinical neuropathy appeared only in the patients whose renal function deteriorated the most. This study established clearly the relationship between diminishing renal function and the beginning of uremic neuropathy.

From the pathological stand point of you, early studies using standard histopathology methods suggested that the main pathogenesis of nerve lesion was axonal degeneration in a distal distribution (Asbury et al. 17, 21, 22 1963; For no and Alston 1967)19 this concept has been substantiated by more recent quantitative studies by both Dyck and Thomas and their associates, who also pointed out that some demyelination occurs, apparently as a secondary event in fibers in the early stages of Axonal degeneration. Other authours[20] have been more impressed by the demyelinative aspects of neuropathy (Dayan et al., 1970 Dinn and Crane, 1970; Appenzeller et al., 1971) more detailed discussion of the morphologic aspects of uremic neuropathy is undertaken in the section entitled pathologic features.

The studies alluded to in the foregoing paragraphs raise, but do not answer, the crucial questions about uremic polyneuropathy. What is the precise

metabolic defect responsible for the neuropathy? Where and how does it act? Is the specific mechanism in uremic neuropathy also common to other, metabolic neuropathies such as deficiency neuropathies or neuropathies due to toxins? How might dialysis methods be modified to prevent or cure the neuropathy? These questions will direct investigation of this condition in the coming few years.

DEFINITION

Chronic kidney disease is defined as renal injury of a more prolonged nature, often leads to progressive and irreversible destruction of nephron mass, irrespective of cause, the eventual impact of severe reduction in nephron mass is an alteration in function of virtually every organ system in the body.[1]

Causes of Chronic Kidney disease

Vascular

Renal artery stenosis (only when bilateral or affecting solitary functioning kidney)
Hypertensive nephrosclerosis
Systemic sclerosis
Haemolytic uraemic syndrome/thrombotic thrombocytopenic purpura
Vasculitis (polyarteritis, wegener's)

Glomerulopathy

All causes of primary glomerulopathy (Except minimal change)
All causes of secondary glomerulopathy (with associated multi system disease, e.g., SLE, Henoch-Schonlein purpura)
Toxic glomerulopathy (gold, pencillamine)

Tubulointerstitial nephropathy (TN)

Idiopathic
Associated with multisystem disease (Sjogren's, sarcoidosis)
Associated with metabolic disorders (e.g. urate, nephrocalciniosis)
Toxic e.g. analgesic abuse, Bence-Jones' protein in myeloma

Infection
Chronic pyelonephritis
Renal tuberculosis

Cystic disease
Adult polycystic disease

Obstructive nephropathy
Diabetic nephropathy
Amyloidosis
Renal dysphasia, hyperplasia, agenesis

KDOQI staging of chronic kidney disease

Stage	Description	GFR ml /mt per 1.73 m^2
1.	Kidney damage with normal GFR or increased GFR	90
2.	Kidney damage with mildly decreased GFR	60-89
3.	Kidney damage with moderately decreased GFR	32-59
4.	Kidney damage with severely decreased GFR	15-29
5.	Renal failure	< 15

Technically, measurement of total glomerual filtration rate is not possible, alternatively creatinine clearance test must be followed to assess the approximate values of total glomerular filtration rate even though if there is a slight difference from the above.

1. Cockcroft – Gault Equation

$$\frac{(140 - \text{age}) \times \text{Body weight in Kg}}{72 \times \text{Pcr (mg/dl)}}$$

2. Equation from the modification of diet in renal disease study

Estimated GFR $= 1.86 \times (\text{Pcr})^{-1.154} \times (\text{age})^{-0.203}$

CLINICAL FEATURES OF UREMIC NEUROPATHY

Neuropathy occurs in atleast 65% of patients who are about to begin dialysis for chronic kidney disease and is perhaps the most common neurological consequence of chronic uremia. It is a distal, symmetrical, mixed sensory motor polyneuropathy affecting the lower limbs[27] to a greater extent than the upper limbs. It is clinically indistinguishable therefore from the neuropathies associated with chronic alcohol abuse, diabetes mellitus, and lupus erythematosus to name but a few.

The rate of progression, severity, prominence of motor or sensory signs, and prevalence of dysesthesia are quite variable. Males are developing neuropathy with an incidence several fold greater than females; this difference is unexplained. Individual serological, biochemical abnormalities (Calcium, Magnesium, Phosphate, Urea, creatinine) are not correlated well with this or any other neurological manifestation of the uremic state. The chronicity and severity of kidney disease appear to be the important cause to the development of neuropathy.

The restless leg syndrome[28] occurs commonly in uremic patients and probably heralds peripheral nerve involvement by the Uremic process. The syndrome consists of creeping, crawling, prickling, pruritic sensations deep within the lower limbs, which are almost always worst in the evening and are relieved by movement of the limbs[29].

These unpleasant sensations are usually localized to the legs but occasionally occur in the thighs and feet as well as in the upper limbs.

The pathogenesis of the restless legs syndrome is not clear. Peripheral nerve dysfunction probably gives rise to the syndrome. It has been described in association with diabetic neuropathy, avitaminosis & carcinoma. Circumstances in which peripheral neuropathy function is often impaired, however restless legs has also occurred in barbiturate withdrawal. Exposure to cold, prochlorperazine therapy and pregnancy and the symptoms are aggravated by concurrent depressive reactions the precise origin of the disorder remain unclear.

Burning feet identical to that phenomenon encountered in alcoholics and in arsenical neuropathy has been described as an early manifestation of uremic neuropathy. Unpleasant tingling, band like constrictions, swelling sensations

and tenderness in the distal extremities are some of the paresthesias described by the majority of patients with early uremic neuropathy.

Muscle cramps of the distal limbs occur commonly in uremic patients and many of these patients lack evidence of neuropathy or tetany. [30]Since cramps occur commonly in uremia. They probably represent either shifts of fluids into muscle or the effects of uremic toxins upon muscle or the neuromuscular junction. Impaired vibratory sense in the lower limbs, loss of deep tendon reflex and ankle jerks followed by knee jerk is the usual first signs of uremic neuropathy. The rate of progression of neuropathy varies widely among patients; in general it evolves over several months and the upper extremities may become involved. On occasion a fulminant course occurs and some patients develop a disabling flaccid quadriplegia. In some patient's distal weakness, muscle atrophy and sensory loss progress over several months then plateau and remain stationary despite worsening of kidney disease. The factors that determine these differences in the clinical course of neuropathy are unclear.

PATHOGENESIS OF UREMIC NEUROPATHY

The observation that uremic neuropathy improves with haemodialysis has led most observers to conclude that neuropathy result from the accumulation of a dialyzable metabolite. Scrbner[31] has speculated that these substances might be in the middle molecule range, compounds of this size may cross most dialysis

membranes more slowly than smaller molecules such as creatinine and urea which are the usual measures of chemical control of uremia. Thus one might theoretically achieve chemical control of uremia, while failing to remove the putative toxins.

Supporting this contention have been the observations that (1) control of neuropathy may in some cases be dependent upon increased hours of dialysis per week, beyond that which is necessary for chemical control of uremia and (2) some patients maintained on peritoneal dialysis appear to have a lower incidence of neuropathy.

Such observations suggest that the peritoneal membrane may permit passage of some toxic molecules more readily and selectively that the cellophane membranes used in hemodialysis. In one study, however, in which 5 uremic patients with neuropathy and 25 without neuropathy were studied, the correlation between a calculated middle molecule concentration and the presence of neuropathy was poor. The “middle molecule” hypothesis is thus attractive but there is as yet little rigorous evidence to support it.

How a dialyzable toxin might produce neuropathy is of some interest. A suggestion that transketolase[33, 34] a thiamine – dependant enzyme in the pentose phosphate shunt, found in erythrocytes, neural tissue, and elsewhere, is inhibited

by uremic toxins" was intriguing because of the clinical and pathological similarities between uremic and thiamine-deficiency neuropathy. However, several groups have failed to find any alterations of erythrocyte transketolase[34] activity in uremic patients before or after hemodialysis.

Because of the varying nutritional status of uremic patients, the possibility that vitamin deficiency is a mechanism of neuropathy should be considered. Massive doses of vitamins administered both orally and parenterally have failed to influence clearly the course of neuropathy in informal trails. This experience has led to general agreement that uremic neuropathy is not a result of vitamin deficiency. Elevations of plasma myoinositol levels in uremic patients have led to speculation that this compound bears on the problem of neuropathy. Myoinositol [37] is a water-soluble, cyclic hexitol, with a molecular weight of 180. It is a precursor of the phosphoinositides. A class of phospholipids whose rapid turnover in neural tissue has resulted in speculation linking their metabolism to the functional activity of nerve. The kidney probably plays an important role in both myoinositol metabolism and excretions. Hypermyoinositolemia has been produced in rats with a diet that contains 35 percent myoinositol;38 slowed motor nerve conduction velocities were induced in the sciatic nerves of these animals. Conduction velocities became normal after a normal diet was instituted. However, the possibility that elevated plasma myoinositol levels

may play a role in the pathogenesis of urmeic neuropathy must be evaluated further.

An inhibitory effect of uremic toxins upon endoplasmic flow of transmitters or other essential neural nutrients, as has been shown by pleasure et al, for acryl amide-induced neuropathy. Is an interesting possibility which has not yet been tested?

PATHOPHYSIOLOGY OF UREMIC NEUROPATHY

Some confusion regarding the essential morbid anatomy of uremic neuropathy appears to have been created by several studies. In which the demyelinative aspects of the neuropathy were emphasized and the disorder was widely presumed to be caused by a metabolic dysfunction of Schwann cells. However, the original clinical and pathological description of the disorder by Asbury, victor, [20, 21, 22] and Adams has now been amply corroborated and appears to be a primary axonal degeneration with secondary segmental demyelination; the segmental loss of myelin is consequent to an abnormality in the axon cylinder, which most likely reflects a metabolic failure39 of the perikaryon. The pathological findings are not specific for uremia; they are more easily distinguishable from the findings in alcoholic neuropathy, for example, another axonal degeneration which is also more severe in the distal aspects of the neuron. All fiber sized, both myelinated and unmyelinated, are affected, although the largest and most distal fibers are selectively vulnerable, Segmental

demyelination occurs in those fibers about to undergo breakdown, although nerve fibers degeneration rapidly probably by pass the demyelinative phase. Qualitative changes seen on electron microscopy include splitting of the myelin lamellae and separation from the abnormalities, and the occurrence of membrane-bound collections of glycogen particles in the axonal space as well as occasional densely lamellate sausage shaped structures. No consistent abnormalities of microfilaments or neurotubules were recognized. These changes are abnormal but not distinctive for uremic neuropathy.

POTENTIAL "UREMIC NEUROTOXINS"

Metabolic products:-

Urea, amino acids, amines, organic acids, indoles, phenols, creatinine, uric acid, myoinositol, sorbitol, sulfates, polyamines, middle molecules.

Guanidine compounds:-

Methylgunidine, guanidine, guanidinosuccinic acid, guanidinoacctic acid, guanidinoproprionic acid, glycocyamine, guanidinobutyric acid.

Peptides, hormones, and enzymes:-

Parathyroid hormone, calcitonin, glucagons, natriuretic peptide growth hormone, renin, gastric, transketolase deficiency, thiamine definiciency.

Trace elements:-

Aluminum, tin, lead, cadmium, zinc, mercury, manganese, arsenic, copper, iron.

ROLE OF UREMIC TOXINS

The etiology of uremic neuropathy remains unclear. Most theories have centered on the role of any of a multitude to "uremic toxins" a partial list of uremic toxins currently being investigated.

Any or all of the agents in table may play a role in the development of uremic syndrome. Despite the vehemence with which various groups of investigators defend the prosperities of these substances, the evidence that any of these agents are themselves bonafide toxins is poor. For example the entire theory of the toxic effects of "middle molecules" appears to be based on short-term observations in a few patients. Basic investigation of the possible toxicity of middle molecules is sparse although much basic work has been done on their identification and quantification. In a recent review, evidence that middle molecules were neurotoxin in patients or laboratory animals was found to be generally lacking.

UREMIC TOXINS AND NERVE CONDUCTION

Several "uremic toxins" have been identified whose elevated concentrations in plasma appear to correlate with depression of motor nerve conduction velocity (MNCV) in patients or laboratory animals[42]. however,

these studies do not take into account that (a) depressed MNCV is cyclical, with abnormally low values one day and normal values the next, (b) there is day-to-day variation in MNCV which approaches 20 percent and (c) the findings of depressed MNCV in laboratory animals associated with high plasma levels of potential “Uremic neurotoxins” has generally not been conformed in human subjects with renal failure[43].

Other uremic toxins have been singled out because their levels in blood correlate with depression of MNCV in patients with kidney disease. Such analysis’s have been applied to plasma levels of urea, creatinine, parathyroid hormone (PTH), myionositol, transketolase, guanidine derivatives, and middle molecules, and even in the presence of intact kidneys72 ,73,74 however, Nielsen47 suggested that for a substance to be a uremic neurotoxin, its blood levels should correlate better with a particular manifestation of peripheral nerve dysfunction(such as reduced conduction velocity) than with a simple reduction in GFR, although it is possible to correlate impairment in MNCV with levels in blood of various substances, the best correlation was obtained between reduced MNCV and a reduction in GFR, with a coefficient of correlation (r value) of 0.68 to 0.84. it was stated that for a substance to be a uremic neurotoxin it should have a better correlation with MNCV than does a reduction in GFR. As can be seen in the Table, nothing correlates better with reduced MNCV than GFR.

PARATHYROID HORMONE (PTH)

Among the potential uremic neurotoxins, the substance which has probably received the most recent attention has been PTH. It has been suggested that may be a uremic neurotoxin based on a correlation between plasama PTH levels and MNCV in patients with chronic kidney disease, as well as possible effect of PTH levels and MNCV in patients with chronic kidney disease, as well as a possible effect of PTH on MNCV in dogs[42] one way to determine the effects of PTH on nerve function is to evaluate nerve function in patients who have primary or secondary hyperparathyroidism without kidney disease. Several such studies have been carried out. Pattern and co-workers found that in 16 patients with primary hyperparathyroidism. MNCV was normal and following parathyrodiectomy there was no change. Furthermore, in six patients who have secondary hyperparathyroidism, the MNCV was also normal and was not altered by medical treatment of the secondary hyperparathyroidism. 49Thus, in patients who have hyperparathyroidism with uremia, there is no observable effect of PTH on peripheral nerve function.

If PTH actually is a Uremic Nerurotoxin and has a rapid effect on nerve function, this should be evident in patients or animals with acute kidney disease. In 12 patients with acute kidney disease, levels of PTH were more than three times the normal value. Moreover, it was found that in these same patients, the MNCV was normal, despite the elevated PTH levels. The normal MNCV was

not affected by dialysis for 2 to 6 weeks, nor by the diuretic phase of acute kidney disease. In fact, when the same patients were tested 3 months, after recovery of renal function, when PTH levels were normal, MNCV was unchanged. Thus, hyperparathyroidism does not noticeably affect nerve function in human with acute kidney disease.

Several studies have examined the relationship between plasma PTH levels and MNCV in patients with chronic kidney disease. Although Avram and co-workers found a relationship between plasma PTH levels and MNCV in uremic subjects, this was not confirmed by another group workers. The data of this latter group are summarized. In 35 Uremic patients treated latter group are summarized in 35 Uremic patients treated with chronic haemodialysis, the MNCV was no change in MNCV. A similar pattern was suggested by the studies of Teschan and co-workers. They followed 72 patients for up to 12 months. In their patients population, at the time dialysis was begun, GFR exceeded 10ml/Min.

These patients has normal predialysis MNCVs and these were unaffected by dialysis. Thus, in patients with either acute or chronic kidney disease, nerve conduction velocities were normal despite high plasma levels of PTH. There was no change of MNCV as a result of either recovery of renal function or chronic haemodialysis; there was also no effect of parathyroidectomy. In addition, it is general experience that when patients begin dialysis therapy,

MNCV either stabilizes or improves. However, virtually all of these patients have elevated plasma PTH levels. This further suggests lack of any effect of PTH on nerve function. Several studies of the effects of PTH on MNCV in dogs have also been carried out. Although one study showed a fall of MNCV in dogs ARG, others suggested that MNCV is normal in dogs with kidney disease for 3,5 days and is in fact unaltered after kidney disease of 6 months duration.

NERVE CALCIUM AND MYELIN

It has also been suggested that nerve Ca+2 might rise in animals with kidney disease as a consequence of excess amounts of PTH in blood42. however, in preliminary studies it was found that nerve Ca+2 declines in animals with kidney disease and is abnormally low in dogs with kidney disease for periods of 3,5 days to 6 months. It is appropriate that this should happen. Several studies have revealed that most of the Ca+2 in peripheral nerves is present in the myelin.

Additionally, studies from several laboratories have shown that the histology in uremic nerve includes, as one of it s most prominent manifestations, loss of myelin. If there is a loss of myelin51. Then nerve ca+2 which are probably extensively bound to protein and phospholipids, should fall. The concentration of Ca+2 in axonal fluid is probably transported by means of calcium –binding protein in nerve. In fact, a decrement of Ca+2 in nerve

decreases intraxonal transport by 60 to 80 percent in vitro, contrariwise, increased nerve Ca+2 actually increases transport in nerve axons in vitro. Thus, it is reasonable to assume that a decrement in MNCV might occur as a consequence of a fall in Ca+2 content in nerve. This is what appears to happen. An increase of nerve Ca+2 might be expected to result in an increase of MNCV. Thus, at the present time, none of the so called uremic toxins can be shown to affect peripheral nerve function. Rather, the majority of evidence suggests that Uremic neuropathy is related to anatomical nerve damage, which taken months to years to develop objective evidence of nerve dysfunction is generally not present when GFR exceeds 10ml/min. The evidence that parathyroid hormone plays an important role in the nerve dysfunction is unconvincing. But recent studies support the middle molecular theory for the basis of occurrence of Neuropathy.

Nerve conduction study

Nerve conduction studies allow localization of compressive focal neuropathy and detection of polyneuropathy, with distinction between demyelination; axonal degeneration and conduction block neuropathies. Electromyography detects denervation of muscle, helps to distinguish between myopathic and neuropathic weakness, and is diagnostic of myotonias and neuromyotonias. Single-fiber electromyography and neuromuscular

transmission studies are particularly important for diagnosing myasthenia gravis and the Lambert Eaton myasthenic syndrome.

Motor conduction studies

Maximal motor conduction velocity is measured by applying a supramaximal stimulus to a motor nerve at two or more different points along its course through bipolar electrodes applied to the skin over the trunk of the nerve. The evoked compound muscle action potential from a muscle supplied by this nerve is recorded. Measurement of the latency from the stimulus to the initial rise of the compound muscle action potential, and of the distance between the pairs of stimulating electrodes, allows calculation of the conduction velocity in m/s along various segments of the nerve. In the case of the median nerve the interval between the stimulus applied at the wrist and the initial rise of the muscle action potential in the abductor pollicis brevis is known as the distal motor latency. Motor conduction velocities generally exceed 48m/s in the arms and 40 m/s in the leg nerves. Distal motor latencies (DMLs) vary depending upon the particular nerve, the site of stimulation, and the technique employed, for the median nerve following stimulation at the wrist, the normal DML is less than 4.2 m/s vary depending upon the particular nerve, the site of stimulation, and the technique employed for the median nerve following stimulation at the wrist, the normal DML is less than 4.2m/s but will be prolonged in carpal tunnel syndrome or demyelination neuropathy. F-wave latencies, which reflect the

time taken for the antidromic volley to depolarize the motor neuron cell bodies within the spinal cord, and then for the passage of the resultant action potential to travel orthodromically to the muscle, reflect conduction over proximal segments of the nerve and root and the normal values are dependent upon height.

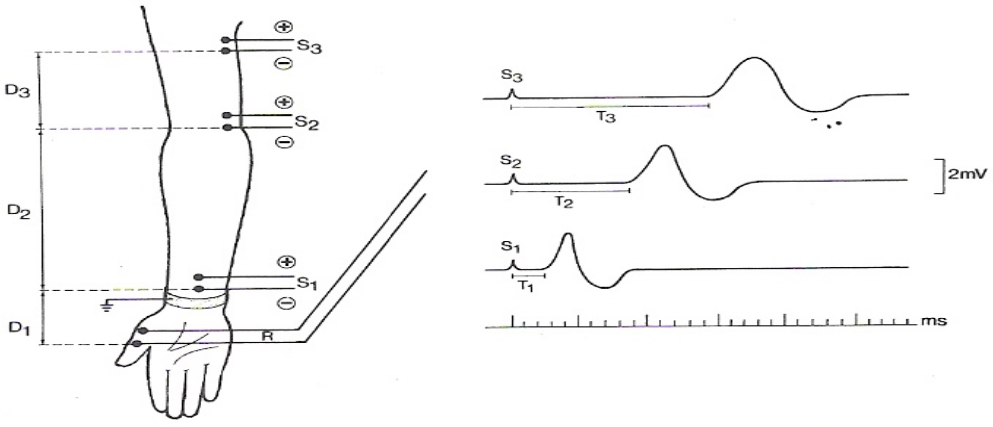

Fig. 2.17. Measuring motor conduction velocity along the median nerve: diagrammatic representation with stimulating electrodes (S_1, S_2, S_3) at various points along the course of the nerve and measurement of the compound muscle action potential using surface electrodes (R) over abductor pollicis brevis (reproduced from Bradley 1974).

Well established methods are now available for studying motor conduction in the median, ulnar, and radial nerves in the arm, and in the common peroneal and posterior tibial nerves in the leg, and the normal ranges for motor conduction parameters have been extensively documented (Liveson and Ms 1992 Binnle *et al.* 1995): Temperature has a profound effect upon nerve conduction, so the skin temperature of the limb should be maintained at

25-30 ^{o}C, if necessary by prior immersion in warm water or by a radiant heat lamp.

Blockade of impulse conduction is recognized increasingly as an important cause of weakness due to peripheral nerve disease. This conduction block usually reflects failure of action potential propagation through axons at sties of severe compression or through segments that are demyelinated. It is especially seen in acutely demyelinated nerves within the first few weeks before sodium channel redistribution to the denuded internodal segments of the axon allows resumption of conduction, albeit at slowed velocity. Recently it has been recognized that there are neuropathies in which conduction block appears to be the primary pathophysilogical process. In such neuropathies, the block often occurs without sufficient associated conduction slowing to point to underlying demyelination; multifocal neuropathy with conduction block (section 12,11,13) is an important example. Most frequently, conduction block is partial rather than total and it may be diffusely distributed along a length of nerve, rather than being tightly localized to a particular site.

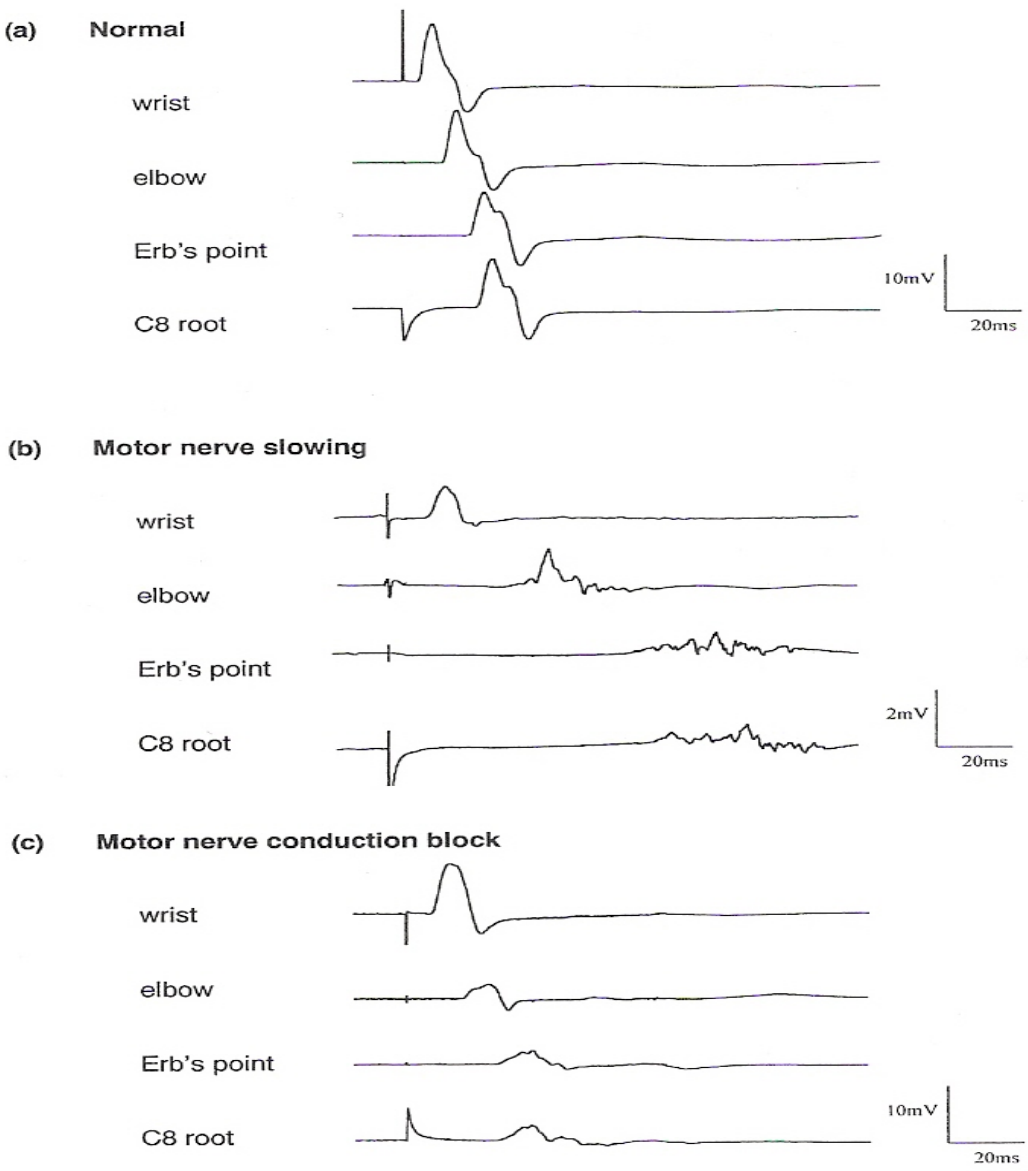

Fig. 2.18. Abnormalities in motor conduction along the median nerve recorded with surface electrodes over abductor pollicis brevis. (a) Normal, showing constant amplitude compound muscle action potentials (CMAP) with normal latency. (b) Demyelinating neuropathy, showing slowing and dispersion of CMAPs. (c) Multifocal motor neuropathy with conduction block in the forearm segment, causing reduced CMAP amplitudes following stimulation at the elbow and above, but with preserved conduction velocity (courtesy of Dr M. Busby).

This has led to difficulty and dispute about the quantificative definition of conduction block. Patial conduction block leads to three electrophysiological abnormalities;

1. Reduced amplitude and area of the compound muscle action potential evoked by nerve stimulation at proximal sites compared to distal different authors quote degrees of reduction ranging from 20 to 60 percent (Lewis and summer 1982 Cornblath *et al.* 1991).

2. Dispersion of the compound muscle action potential wave form; however, this abnormal temporal dispersion can lead to phase cancellation, resulting in the misleading appearance of amplitude reduction of the compound muscle action potential.

3. Absent or sparse F-wave responses if the conduction block affects proximal nerve segments or the nerve roots.

Sensory nerve action potentials

Sensory conduction in the median, ulnar, and radial nerves can be measured by applying stimuli through ring electrodes upon a finger and then recording the sensory nerve action potential through cutaneous electrodes applied over the trunk of the nerve (orthodromic conduction). For other nerves, such as the sural, the nerve trunk is stimulated and sensory nerve

action potentials recorded from surface electrodes (antidromic or orthodromic conduction). The sensory nerve action potential (SNAP) is so small that averaging techniques are required following multiple stimuli, and occasionally needle recording electrodes inserted close to the nerve are required (Kimura 1983; Liveson and Ma 1992; Binnie *et al.* 1995).

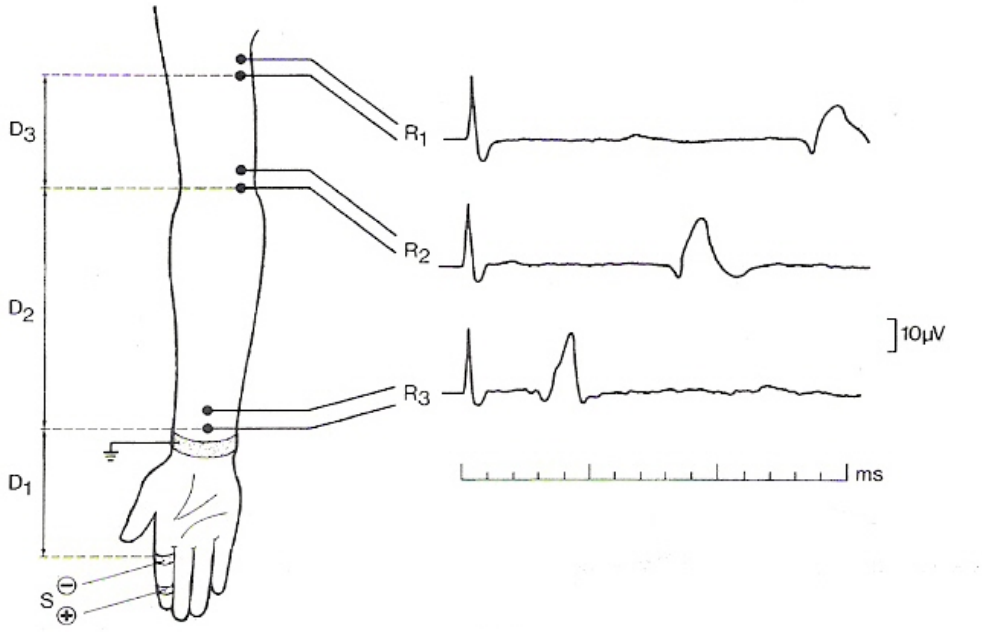

Fig. 2.19. Diagrammatic representation of the technique of measuring the sensory nerve action potential (SNAP) in the median nerve (at points R_1, R_2, R_3) after orthodromic stimulation of the finger(s) (reproduced from Bradley 1974).

Sensory nerve action potential amplitudes generally range from 5 to 50 μV, depending upon the particular nerve being studied, and drop in amplitude, or absence of the potential, occurs in axonal degenerative, demyelinating, or compressive neuropathies. Thus a diminished SNAP cannot in itself distinguish between these types of neuropathy. Sensory nerve action potentials reflect the integrity of the distal axonal branch of the dorsal root ganglion sensory neurons. They remain normal in disease such as spondylitic radiculopathy affecting the spinal nerve roots containing the proximal axonal branch of the dorsal root ganglion cell bodies lie outside the interverbral foramina (Aminoff et al. 1985). The only exception to this can occur in the lower lumbar and sacral nerve roots, in which the dorsal root ganglia can lie within the intervertabral foramina and loss of sensory nerve action potentials, may occur with spinal disease as well as with peripheral nerve disease. Radiculopathy may be confirmed by the finding of denervation within limb and paraspinal muscles innervated by the same segment. Sensory nerve conduction latencies and velocities can be measured but generally find little usefulness in diagnostic clinical practice. Routine techniques for measuring possible conduction block in sensory nerves have not been established.

Uses of nerve conduction studies

Nerve conduction studies are principally used to diagnose focal monoeuropathies, usually due to nerve compression, and to detect polyneuropathy and determine whether it is due to demyelination or axonal degeneration. The additional uses of detecting conduction block neuropathies and in discriminating nerve root disease from polyneuropathy are dealt with above.

Focal compressive neuropathy

Focal compressive neuropathy can be diagnosed electrophysiologically for most limb nerves and some truncal nerves. This is particularly useful for median nerve compression in the carpal tunnel and the ulnar nerve at the elbow. Conduction distal to a neuropraxial lesion of a peripheral nerve may remain normal at a time when its function is severely impaired. When a nerve is compressed, as in entrapment neuropathies, motor and sensory conduction across the site of the lesion may be either lost or greatly reduced in speed. This leads to reduction or loss of the sensory action potential in that nerve, and prolongation of the distal motor latency. Localized slowing of motor conduction can be demonstrated at some entrapment sites, such as compression of the ulnar nerve at the elbow, and techniques are now available for measuring conduction over short segments

of nerve in presumed entrapment neuropathies (liveson and Ma 1992). Electromyographic sampling of muscles supplied by a trapped nerve will show to what extent axonal degeneration has caused denervation. This generally implies a poorer prospect for recovery of nerve function following surgical release of the compression.

Changes in the electromyogram (EMG), tactile sensibility, and nerve conduction after suture or compression of peripheral nerves in human subjects have been studied longitudinally (Buchthal and Kuhl 1979). Enlargement of re-innervated motor units and marked dispersion of motor unit action potentials persisted long after suture. The sensory nerve action potential recovered five times as quickly, and tactile sensibility 10 times, after correction of a compressive lesion as after releasing a suture. After relief of compressive lesions, the maximum motor and sensory conduction velocity recovered to 80-90 percent of normal within 1 year, but after nerve suture it had only reached 65-75 percent of normal after 40 months.

Demyelinating polyneuropathies

Demyelinating polyneuropathies markedly slow conduction along affected nerve trunks. Sometimes difficulty can arise because reduced velocities are seen in profound axonal loss when there is no surviving fast – conducting fibers remaining to a grossly denervated muscle. If demyelination

chiefly affects the proximal segments of motor fibres, it will be associated with normal conduction velocity measurements along distal segments. In this case, prolonged F-wave responses are a clue to proximal conduction slowing. Criteria have been proposed for defining a neuropathy as demyelinating in nature (ad Hoc subcommittee of American academy of Neurology AIDS Task Force 1991) in outline these require three out of four of the following abnormalities, affecting tow or more nerves:

1. Reduction of motor velocity to less than 80 percent of the lower limit of normal (which represent <39 m/s for arm nerves and <34 m/s for leg nerves);

2. Partial conduction block of greater than 20 percent or abnormal temporal dispersion causing greater than 15 percent change in duration not attributable to an entrapment neuropathy;

3. prolonged distal motor latencies exceeding more than 125 percent of the upper limit of normal;

4. Prolonged F-wave latencies greater than 125 percent of the upper limit of normal.

Such stringent criteria, while useful in established disease, are not met early in the course of mild forms of chronic idiopathic demyelinating

polyneuropathy. Furthermore, sometimes these criteria can only be satisfied by exhaustive electrophysiological study of numerous individual peripheral nerves. Most demyelinating neuropathies also involve sensory fibers, with reduced amplitude or absent sensory nerve action potentials.

Axonal degeneration polyneuropathies

Axonal degeneration polyneuropathies usually involve a dying back process which mainly affects the longest axons. The earliest evidence of axonal polyneuropathy is electromyographic evidence of denervation of foot and hand muscles, coupled with reduced amplitude or absence of sensory nerve action potentials in the feet and hands. The muscle denervation is evident on surface electromyography by reduction in the amplitude of compound muscle action potentials, which normally range from 10 to 25 m V in hand muscles. Concentric needle electrodes inserted into denervated muscle will reveal fibrillation potentials and positive sharp waves. Early on the motor conduction velocity in surviving axons will be normal, or only marginally reduced. However, as severe denervation sets in and the large-diameter axons are lost, the motor conduction velocity can fall markedly but rarely to less than 80 percent of the lower limit of normal and the distal motor latency can rise, but rarely above 125 percentage of the upper limit of normal (Corbnlath *et al* 1992).

This means that primarily demyelinating polyneuropathies can be distinguished electrophysiologically from axonal degeneration. However, in practice, a number of polyneuropathies involve mixed elements of demyelination and axonal degeneration and sometimes evade confident clinical or electrophysiological classification into either category.

MATERIALS AND METHODS

The study was conducted at the medical wards of Tirunelveli medical college hospital, Tirunelveli during the period of May 2004 – May 2006 Patients with proved clinical, bio-chemical parameters in favour of chronic kidney disease are included in this study. All patients included in this study were not on dialysis.

Inclusion criteria for chronic kidney disease

1. Serum creatinine more than 2 mg %
2. Creatinine clearance < 40 ml /mt

Calculated using the formula

Cockcroft – Gault Equation

$$= \frac{(140 - \text{age}) \times \text{Body weight in kg}}{72 \times \text{Pcr (mg/dl)}}$$

3. Ultrasound abdomen – kidney size < 9 cm

Exclusion criteria: Patients with other recognizable risk factors for peripheral neuropathy are excluded from the study.

Diabetes mellitus

Alcoholism

Drug induced peripheral neuropathy

Hansen's disease

Totally 74 patients were studied. The duration of renal failure varies from 3 months to 7 years.

A detailed history was taken in all patients with special reference to

1. Renal symptoms like scanty micturition

Swelling of legs, face

Loss of appetite

Nausea, vomiting and

Pruritis.

2. Symptoms in favour of peripheral nerve involvement like

numbness

pins and needle sensation

defective appreciation of pain and

weakness, thinning of muscles were also asked for.

3. Symptoms suggestive of autonomic disturbances like

absence of sweating,

variation of skin temperature,

postural giddiness,

post micturition dribbling,

fecal incontinence,

defective sexual dysfunction in the form of failure of erection or ejaculation were elicited.

4. An elaborated clinical examination was done in all patients with special reference to anemia, skin changes, peripheral nerve thickening, sensory and motor signs (especially ankle reflex) were looked for.

5. Bio-chemical parameters pertaining to renal dysfunction like

Blood urea

Serum creatinine

Creatinine clearance

Serum electrolytes were done for all patients.

Blood hemogram, urine analysis, X-ray chest, and ECG were taken for all these patients.

Supportive evidences like diagnostic ultrasound is taken as a diagnostic tool to assess the size of the kidney as kidneys are contracted in chronic kidney disease. Normal kidney size ranges from 9 to 12 cm. In chronic medical renal disease, the size of the kidney is usually less than 9 cm.

After selecting the patients with reference to inclusion and exclusion criterias, the presence of peripheral nerve dysfunction is assessed in them

1. CLINICALLY by means of motor and sensory symptoms and signs.
2. ELECTROPHYSIOLOGICAL STUDIES – Nerve conduction studies

Clinical features like peripheral sensory loss, pin and needle sensation, burning feet sensation, distal muscle weakness and distal reflex loss are taken as indicators of clinical peripheral nerve dysfunction.

Nerve conduction studies are done in all patients.

A suitable nerve is selected so that it can be stimulated at two points along its course and the response is recorded by using the surface electrodes placed over the muscle, supplied by that particular nerve.

The following nerve conduction studies were performed in all patients on all 4 limbs.

Motor nerve conduction study of Median nerve

Ulnar nerve

Peroneal nerve

Tibial nerve

Sensory conduction study of Median nerve

Ulnar nerve

Sural nerves were done in all patients.

In the motor nerve conduction study, the distal latency, amplitude of compound muscle action potential conduction velocity and latency of F waves were studied. In the sensory conduction study the latency and amplitude of sensory action potential were studied.

The following criterias are taken as evidences of peripheral neuropathy.

MOTOR NERVE CONDUCTION VELOCITY

- **Motor nerve conduction velocity < 40 m/sec**
- **Delayed distal latency**
- **Fall in amplitude of compound muscle action potential > 30% between proximal and distal stimulation.**

SENSORY NERVE CONDUCTION VELOCITY

- **Delay in peak latencies.**
- **Reduced sensory nerve action potential.**

Statistical analysis was done with inference using students T test, chi square and averages.

OBSERVATION

TABLE 1

NO OF PATIENTS AFFECTED VERSUS TOTAL NUMBER OF PATIENTS ASSESSED IN PERCENTAGE

Total No. Of Patients	Patients With Peripheral Nerve Dysfunction
74	48 (65%)

Numbers of patients affected with chronic kidney disease were 74.

Out of 74 patients assessed, 48 patients proved to have peripheral nerve dysfunction by electrodiagnostic study.

TABLE II

NO OF PATIENTS AFFECTED MALE AND FEMALE VERSUS TOTAL

NUMBER OF PATIENTS AFFECTED

Total No Patients With Peripheral Nerve Dysfunction	No. Of Male	No Of Female
48	36	12

The numbers of patients with peripheral nerve dysfunction were 48.

Among these, 36 patients were male and 12 were female.

TABLE III

Peripheral nerve dysfunction and age group

NUMBER OF PATIENTS AFFECTED WITH REFERENCE TO AGE GROUP

Age group	Total	Affected
15-24	10	6
25 to 34	12	11
35-44	21	13
45 to 54	17	10
55-64	8	3
65-74	6	5
Total	74	48
Mean	42.6	41.7
S.D	14.3	14.6

P > 0.05

6 patients affected were in the age group 15 – 24 years, 11 patients in the age group 25 – 34 years, 13 patients in the age group 35 – 44 years, 10 patients in the age group 45 – 54 years, 3 patients in the age group 55 – 64 years, 5 patients in the age group 64 – 74 years The above table reveals that the affected patients are more in the age group 35 – 44 years.

TABLE IV

NO OF PATIENTS AFFECTED BY PERIPHERAL NERVE DYSFUNCTION IN CHRONIC KIDNEY DISEASE VERSUS DURATION OF DISEASE

Duration of chronic kidney disease	Total no of patients	No patients with p.n. dysfunction
< 1 years	11	4(36%)
1-3 years	21	11(52%)
3-5 years	22	16(73%)
>5 years	20	17(85%)
TOTAL	74	48

Chi square = 8.125 $p < 0.01$

From this table, it is learnt that the number of patients affected with peripheral nerve dysfunction is increasing when the duration is increasing (more than 5 years). Statistical analysis done using chi square = 8.125 $P < 0.01$ so it is significant.

TABLE V

Type of Peripheral Neuropathy

NUMBER OF PATIENTS AFFECTED WITH PERCENTAGE WITH REFERENCE TO THE TYPE OF PERIPHERAL NEUROPATHY

SENSORY MOTOR	SENSORY	MOTOR	Total
25(34%)	12(16%)	11(15%)	48(65%)

48 patients had evidence of peripheral neuropathy by electro diagnostic study. 25 patients revealed sensory motor neuropathy, 12 patients had sensory neuropathy and 11 patients had motor neuropathy. From the table it is observed that the commonest type of neuropathy in chronic disease patients is distal sensory motor neuropathy.

Table VI

NUMBER OF PATIENTS AFFECTED WITH PERCENTAGE WITH REFERENCE TO OVERT AND SUBCLINCAL NEUROPATHY

OVERT NEUROPATHY	SUBCLINICAL NEUROPATHY	TOTAL
14 (19%)	34(46%)	48 (65%)

Numbers of patients affected with peripheral neuropathy by electrodiagnostic study were 48. Of these 48, only 14 patients showed clinical evidence of peripheral neuropathy. Of these 14 patients 11 patients had both motor and sensory symptoms in the form of loss of ankle jerk and defective vibration sense, 2 patients had numbness both lower limbs, 1 patient had distal muscle weakness of lower limbs.

TABLE VII
NO OF MALE AND FEMALE PATIENTS AFFECTED WITH REFERENCE TO CREATININE CLEARANCE

Creatinine clearance ml/mt.	Total no. of patients		Affected male	Female
	M	F		
<15	60%	79%	72%	66%
15-29	31%	11%	20%	25%
30-59	9%	10%	8%	8%
Total	100	100	100	100

72% of males and 66% of females were affected when the creatinine clearance was < 15ml/mt. 20% of males and 25% of females were affected when the creatinine clearance was 15 – 29 ml/mt. Males were affected more when the creatinine clearance <15 ml/mt. Both sex were affected equally when the creatinine clearance between 30 -59 ml/mt.

From this table, it is observed that 72% of males and 66% of females with creatinine clearance below 15ml/mt showed evidence of peripheral neuropathy.

DISCUSSION

Peripheral neuropathy is a recognized complication of renal failure. This study enlightens the incidence and clinical presentation of peripheral nerve dysfunction in patients with chronic kidney disease.

Total numbers of patients studied were 74. Among the 74 patients 48 patients showed evidence of peripheral nerve dysfunction either clinically or electrophysiologically. 36 male patients showed features of peripheral nerve dysfunction and 12 female patients had evidence of peripheral nerve dysfunction. From the available data there is some predilection for male in the incidence of peripheral neuropathy in patients with chronic kidney disease. When creatinine clearance was <15 ml/mt.

The duration of chronic kidney disease varied from 3 month to 7 years. 85% of patients showed features of peripheral nerve dysfunction either clinically or electrophysiologically when the duration of chronic kidney disease is more than 5 years. This shows that there is a linear correlation between the incidence of peripheral neuropathy and duration of chronic kidney disease. Patients who were presenting with end stage renal failure had creatinine clearance less than 15 ml/mt, the incidence of peripheral nerve dysfunction was more in these patients than in patients in whom the creatinine clearance less was between 15 -30ml/mt.

Jairam, N.Kumar, P.P. Varma discussed nerve condition study in relation to duration and severity and chronic kidney disease. They found that reduced motor nerve conduction velocity and sensory nerve conduction velocity are suggestive of neuropathy but delayed F waves and H reflex are also suggestive of neuropathy.

In this study reduced motor nerve conduction velocity and sensory nerve conduction velocity are markers of peripheral neuropathy. This study doesn't account F waves and H reflex since these are essential for root lesions.

The common type of peripheral neuropathy observed in this study was distal symmetrical sensory motor peripheral neuropathy and incidence of this type of sensory motor neuropathy was 34%. The incidence of sensory neuropathy was 16% and motor neuropathy was 15%. The other types of neuropathy mononeuropathy, truncal neuropathies and cranial neuropathies are not registered in our clinical study.

Among these 48 patients, 34 patients had evidence of peripheral neuropathy in electrodiagnostic study 14 patients had clinical evidence of peripheral neuropathy. 11 patients had both motor and sensory symptoms in the form of loss of ankle jerk, defective appreciation of vibration sense. This may emphasis earliest clinical sign of neuropathy is loss of ankle jerk. 2 patients had numbness of both lower limbs. 1 patient had distal muscle weakness of both lower limbs. So incidence of overt neuropathy is 19% and subclinical neuropathy is 46%.

By Rakesh H. shah, Meenakshi Khar, NC. Mehta study, the incidence of peripheral neuropathy in chronic kidney disease was 68% and the incidence of overt neuropathy and subclinical neuropathy was 21% and 47% respectively.

In this study the incidence of peripheral neuropathy in chronic kidney disease was 65% and the incidence of overt and subclinical neuropathy was 19% and 47% respectively.

CONCLUSION

1. Incidence of peripheral neuropathy is 65% in patients suffering from chronic kidney disease.
2. Distal symmetrical predominantly sensory motor neuropathy is the commonest type of peripheral neuropathy observed in patients with chronic kidney disease.
3. Loss of ankle reflex and vibratory sensory loss are the commonest clinical signs of peripheral neuropathy in patients with chronic kidney disease.
4. There is predilection for male in the incidence of peripheral neuropathy in chronic kidney disease when the creatinine clearance was below 15ml/mt.
5. Incidence of peripheral neuropathy is having linear correlation with severity and duration of renal failure.
6. Incidence of subclinical neuropathy is about 46% and overt neuropathy is 19%.

SUMMARY

Chronic kidney disease is found to cause peripheral neuropathy in 65% of patients both (19%) overt and (46%) subclinical neuropathy of which distal symmetrical sensory motor neuropathy is common and the incidence of peripheral neuropathy is directly proportional to duration and severity of chronic kidney disease.

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PROFORMA

Peripheral nerve dysfunction study in chronic renal failure

Name

Age/sex

Address

Occ. Income

D.O.A

D.O.D

PROFILE ABOUT RENAL FAILURE

Duration of illness

Symptoms

Scanty urination

Puffiness of face and body

Nausea

Vomiting

Loss of appetite

Weakness of the limbs

Pin and needle sensation, cloth sensation

Defective appreciation of pain and temperature

Numbness

Postural giddiness

Sexual dysfunction

Past history H/o HT,DM,TB

H/o smoking Alcohol

General examinations

Anemia

Jaundice

Pedal odema

Peripheral nerve thickening

Pulse, BP

Examination of CNS higher function, cranial nerves, spino motor system, sensory system.

Investigations

Urine albumin

Sugar

Deposit

Blood TC,DC,Hb

Blood sugar

Blood urea

Serum creatinine

X-ray chest

ECG

Ultra sound abdomen

ELECTROPHYSIOLOGICAL EVALUATION

Conduction velocity

Upper limb

Ulnar nerve	Motor
	Sensory

Median nerve	Motor

Anterior tibial nerve	Motor
	Sensory

Common peroneal nerve	Motor
	Sensory